DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JUN 16 2004

Via Federal Express

WARNING LETTER

Pramod Multani, M.D.
Chairman, Downey Regional Medical
Center Institutional Review Committee
8333 Iowa Street, Suite #200
Downey, California 90241

Dear Dr. Multani:

This warning letter informs you of objectionable practices and activities found during a Food and Drug Administration (FDA) inspection of the Institutional Review Committee (IRC) at Downey Regional Medical Center and requests corrective actions. The inspection took place during the period January 20 through 23, 2004, and was conducted by Ms. Kirsten S. Tharp, an investigator from FDA's Los Angeles District Office.

The inspection was conducted to determine whether the IRC's activities and procedures comply with applicable FDA regulations. These regulations apply to your oversight of clinical studies of products regulated by the FDA. Additionally, it was to determine if corrections had been made to address deficiencies identified in a February 1995 FDA inspection of your IRC.

We have completed our review of the report prepared by the Los Angeles District Office which described and documented deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 56 - Institutional Review Boards (IRBs), and Part 812, Subpart D - IRB Review and Approval. The deviations were listed on the Form FDA-483, "Inspectional Observations," which was presented to and discussed with [redacted] Administrative Director, and others at the conclusion of the inspection. The description of deviations that follows is not intended to be an all-inclusive list of IRC deficiencies.

1. Failure to have and follow adequate written procedures as required by 21 CFR 50.24, 56.108(a) and (b), 56.110, 56.115(a)(6), 812.66, and 814.124

The IRC functions under written procedures found in the Medical Staff Bylaws which were promulgated by the Medical Executive

Committee. This document, adopted February 27, 1987, was last revised/updated in March 2003. These procedures do not meet the FDA requirements for written IRB procedures (i.e., providing sufficient detail regarding how review of research is conducted) in several areas. For example,

- There are insufficient details describing how the IRC conducts initial and continuing review of research studies. (See 21 CFR 56.108(a) & (b))

- There are no procedures describing how the IRC determines the frequency for carrying out continuing review of studies, i.e., how the IRB identifies those studies that would require review more frequently than once a year. (See 21 CFR 56.108(a))

- There is no procedure for handling expedited reviews/ approvals, even though the IRC utilizes the expedited review process. (See 21 CFR 56.108(a) & 56.110)

- There are no procedures for determining whether investigational device studies involve significant vs. non-significant risk devices. (See 21 CFR 56.108(a) & 812.66)

- The procedures lacked details concerning the minimum number of members needed to review and vote on approval of research studies, including the need for there to be at least one non-scientific member present.

- The Bylaws state that a quorum shall consist of 33-1/3% voting members, but in no event less than 3 voting members. If your IRC consists of 11 members, under FDA regulations, a quorum would be 6 members (50% + 1).

- The IRC procedures do not address specifically how adverse events are handled. The approval notifications to investigators state only that any adverse events are to be reported to the IRC immediately, but lack additional details such as criteria for determining what constitutes an adverse event.

2. Failure to meet membership and/or quorum requirements [21 CFR 56.107(d), 56.108(c), and 812.60]

In accordance with 21 CFR 56.107(a) and 56.107(d), each IRB is required to have at least five members with varying backgrounds, must be sufficiently qualified through experience, expertise, and diversity of the members, and have at least one member who is unaffiliated with the institution and not part of the immediate family of a person affiliated with the institution. Unless expedited review is being used, review of research must be conducted at meetings where a majority of IRB members are present, including at least one member whose primary concerns are in nonscientific areas. (21 CFR 56.108(c))

Examples of this failure include, but are not limited to, the following:

- The IRC has been reviewing and approving studies without a member unaffiliated with the institution since at least July 2000.

- The IRC meeting of May 29, 2002, did not meet quorum requirements in that only 4 of 11 members were present. Also, there was no non-scientist member present, as required by FDA regulations.

- Because the educational/professional background of [redacted] was not documented, it is unclear if a "non-scientist" was present at the August 11, 2003, meeting. This same issue applies to the attendance of Bill Hare at the October 24, 2001, meeting.

3. Failure to prepare and maintain adequate documentation of IRB activities in accordance with 21 CFR 56.115(a)(2) and (a)(5)

FDA regulations require that an IRB prepare and maintain adequate documentation of its activities, including, for example: IRB meeting minutes in sufficient detail to show actions taken by the IRB; a written summary of the discussion of controverted issues and their resolution; and a list of IRB members identified by

name, earned degrees, representative capacity, indications of experience sufficient to describe each member's chief anticipated contributions to the IRB, and any employment or other relationship between each member and the institution. (21 CFR 56.115(a))

Examples of this failure include, but are not limited to, the following:

- Records regarding each IRC member's representative capacity, indications of experience in sufficient detail to describe their anticipated contributions to IRC deliberations, and any employment or other relationship between each member and the institution are incomplete. IRC membership listings from July 1, 2000, to June 30, 2004, do not identify affiliation with the hospital for most members, and none of the members had CVs/resumes on file.

- Because the IRC membership listing is incomplete, there were instances where it was unclear whether a non-scientific member was present at IRC meetings where studies were reviewed and approved.

We also observed that many of the deficiencies found during FDA's February 1995 inspection still had not been corrected. This included numerous deficiencies in your IRC's written procedures. For example, during that inspection the IRC committed to develop a procedure for expedited review; however, this did not occur.

Within 15 working days of receiving this letter, please provide this office with written documentation of the specific steps you have taken or will be taking to address the deficiencies noted above. This should include a revision of current policies and procedures and the timeframes within which these procedures will be developed and implemented. Remember that the procedures should describe how the IRC functions/processes are accomplished. Failure to respond may result in further regulatory action, such as that described in 21 CFR 56.120 and 56.121.

Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850, Attention:

Barbara A. Crowl. A copy of this letter has been sent to FDA's Los Angeles District Office, 19701 Fairchild, Irvine, California 92612. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Ms. Crowl at (301) 594-4720, ext. 168.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

William Hare
Chairman, Governing Board
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